Major depressive disorder across the life span

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General introduction

1 MAJOR DEPRESSIVE DISORDER

1.1 CHARACTERISTICS AND DIAGNOSTICS

Major depressive disorder (MDD) is a serious psychiatric disorder, classified in the Diagnostic and Statistical Manual (DSM).[1] Nearly one in five to six adults is expected to experience at least one episode of MDD during their life course.[2,3] Current prevalence rates of 5.2% (persons aged 18-65 years)[2] and 3.3% (65 years and older)[3] have been observed, indicating that one can be diagnosed with MDD at any time during the life span. According to the latest edition of the DSM, the DSM-V,[1] persons are diagnosed with MDD if the following symptoms are present within the same period of at least two weeks: either (1) depressed mood or (2) loss of interest or pleasure, in addition to at least four symptoms out of: (3) significant weight loss when not dieting or weight gain, or decrease or increase in appetite; (4) insomnia or hypersomnia; (5) psychomotor agitation or retardation; (6) fatigue or loss of energy; (7) feelings of worthlessness or excessive or inappropriate guilt; (8) diminished ability to think or concentrate, or indecisiveness (1-8 all nearly every day); (9) recurrent thoughts of death, recurrent suicidal ideation, or (a plan for) a suicide attempt. Symptoms need to be present during the major part of the day, and need to result in limitations in daily functioning. In some cases, the DSM-V criteria for MDD are not met, even though several symptoms have been present for a long period of time. This may fit the criteria of another mood disorder: dysthymia, a more chronic form of depressive disorder but with milder levels of symptoms. Besides the symptoms listed in the DSM-V, MDD is often characterized by a range of other symptoms as well, such as anxious or panic symptoms, bodily symptoms (aches and pains, diarrhoea), future pessimism, and interpersonal sensitivity.[4] This wide range of symptoms is an indication that MDD can present itself in various ways.

1.2 RISK FACTORS

MDD is a complex disorder not only symptom wise, it also has a heterogeneous etiology; an interplay between heritability and genetic vulnerability, personality, negative life events and stress, social factors, lifestyle, and health is often responsible for the onset of MDD (also called the Stress-Vulnerability Model).[5] Intrinsic vulnerability to depression is largely innate,[6] and determined by genetic profile and personality. These risk factors have both been shown to be especially associated with early-onset MDD.[7–10] Most risk factors, however, can occur at any point throughout life and the likelihood of their occurrence differs across the life span. To our knowledge, no studies examined the occurrence of a wide range of risk factors of MDD and their relative impact on MDD across the entire adult life span within one study design.

1.3 COURSE AND CONSEQUENCES

A systematic review conducted by Steinert et al.[11] among adults (i.e. studies that only included adolescent or elderly populations were excluded) showed that 70-85% of depressed persons reached remission at some time point during follow-up. For 10-17% of participants, a chronic course was identified. Licht-Strunk et al.[12] performed a similar

systematic review, but only included studies performed among persons aged 55 years and older. This study found that one in three older persons showed rapid remission, and the same proportion had a chronic course of depression. Comparing these numbers, the course of depression seems to be worse among elderly populations, but no direct studies including younger and older MDD patients and using similar methodology to examine MDD course, have been conducted. MDD is the number one cause of disease burden in high-income countries, and this is expected to become a global phenomenon in the coming decade.[13] Compared to persons without a psychiatric disorder, persons with MDD are more likely to use non-mental health care,[14] as the disease burden is not only caused by severe psychological symptomatology, but is also due to decreased somatic health. MDD has been identified as a contributing risk factor for somatic diseases and health problems such as cardiovascular disease, diabetes, hypertension, stroke, obesity,[15] and even premature mortality.[16] MDD has also been associated with higher levels of loneliness and decreased social support[17] and an unhealthy lifestyle.[18] As can be seen, there may be a bi-directional link between MDD and these factors; risk factors of MDD may also be consequences of MDD.

2 AGING

2.1 CHRONOLOGICAL AGING

In the Western world, gains in life expectancy rates and longevity have been observed, partly because of medical advances that create a shift from somatic diseases being fatal to having a chronic but manageable prognosis.[19] In The Netherlands, life expectancy at birth is expected to shift from 78.8 (men) and 82.7 (women) in 2010, to 83.8 (men) and 88.1 (women) by 2050.[20] In addition, in persons aged 55-64 years prevalence rates of obesity, alcohol use and lower physical activity have increased in the past decades.[21] These trends implicate that aging-related complications will take up a larger proportion of the adult life span. Altogether, there is a growing need for attention and understanding of the aging population in order to maintain quality of life and to reduce costs associated with aging.

2.2 BIOLOGICAL AGING

Chronological aging is accompanied by biological changes. These biological changes may not run parallel to aging in years. Although an increase in years generally leads to decay of bodily functions, there are many factors which can add to acceleration or the slowing down of this process. One way in which biological age can be measured is by the shortening of telomere length (TL). Telomeres are nucleic-acid protein complexes situated at the ends of chromosomes that serve to protect DNA from damage. During cell division, the very ends of chromosomes are not fully replicated, resulting in telomere shortening during each cell division. Once telomeres become critically short they eventually lose their protective function, which in turn could result in cell senescence and apoptosis.[22,23] Although a decline in TL with age is inevitable, a range of factors (such as stress and an unhealthy lifestyle)[24,25] may accelerate the shortening process.

(such as stress and an unhealthy lifestyle)[24,25] may accelerate the shortening process. Shortened telomeres have been associated with onset of cardiovascular disease,[26] dementia,[27] indicators of arterial stiffness,[28] cancer,[29] and mortality.[27,29] Thus, not only chronological age, but also biological age, may be associated with aging-related phenomena to occur.

3 MAJOR DEPRESSIVE DISORDER & AGING

3.1 MAJOR DEPRESSIVE DISORDER & CHRONOLOGICAL AGING

For MDD, generally the same diagnostic criteria and treatment guidelines are used throughout the adult life span. However, late-life MDD is often described as having a distinct etiology. Early depression onset has often been shown to be associated with personality (especially neuroticism),[7–10] and adverse life events.[8,30] In older age, the likelihood for a somatic pathway to depression might increase. Neurobiological factors, such as cerebrovascular disease, neurodegeneration, and inflammation, may impact the response of the brain towards stress, and therefore might increase the susceptibility to depression.[31] There is also evidence that the presentation of depressive symptoms in late-life is more somatic, with psychomotor agitation, hypochondriasis, and general and gastrointestinal somatic symptoms found to be more prevalent in older persons.[32] Thus, differences may exist across the life span in etiology and presentation of MDD, which could affect the prognosis of MDD as well. As studies previously performed on this topic have several limitations or did not directly compare age groups, in this thesis chronological age differences in the presentation, etiology, and course of MDD will be examined.

3.2 MAJOR DEPRESSIVE DISORDER & BIOLOGICAL AGING

It has been suggested that MDD is a gateway to aging-related conditions due to dysregulations of several biological stress systems, such as the immune system,[33] autonomic nervous system, and hypothalamic-pituitary-adrenal (HPA) axis.[34] These disrupted stress systems have been associated with increased levels of oxidative stress, which in turn may accelerate biological aging.[35] The relationship between psychosocial stress and TL has first been shown by Epel et al.[36] in stressed caregivers. In recent years, the association between MDD and TL has been increasingly examined cross-sectionally. Adults under 60 years with MDD have repeatedly been found to have shorter TL compared to non-depressed peers.[37,38] However, some studies could not confirm this finding,[39,40] and associations between TL and characteristics of MDD (such as severity or duration) have been inconclusive as well.[41–43] Associations between MDD and TL have been studied to a lesser extent in older persons, but mostly hint towards absence of the association.[44–46] Altogether, there is some evidence that MDD is linked to accelerated biological aging. As biological aging may be the underlying mechanism causing problems associated with chronological aging, in this thesis we also investigate whether biological age (indexed by TL) is associated with the presentation, etiology and course of MDD.

4 AIMS OF THIS THESIS

AIM 1: To see whether late-life MDD differs in presentation, etiology, and prognosis from MDD in younger persons.

AIM 2: To examine whether biological age is involved in the presentation, etiology, and prognosis of MDD.

5 COHORTS STUDIED

In this thesis, data were used from two longitudinal cohort studies: the Netherlands Study for Depression and Anxiety (NESDA, https://www.nesda.nl),[47] and the Netherlands Study for Depression in Older Persons (NESDO, https://nesdo.onderzoek.io/).[48] Within both cohorts, all participants provided written informed consent, and all Ethical Review Boards of the participating centers provided approval. In chapters 5 and 6, only data from the NESDO study were used. In chapters 2, 3, 4 and 7, data from NESDA and NESDO were combined and analyzed simultaneously.

5.1 NETHERLANDS STUDY OF DEPRESSION AND ANXIETY (NESDA)

At baseline, the NESDA sample comprised 2,981 persons aged 18-65 years with a current (6-month) diagnosis of a depressive and/or anxiety disorder (n = 1,701), a remitted depressive and/or anxiety disorder (N = 628), or no history of depressive and anxiety disorders (n = 652). Recruitment took place in the general population, primary health care and outpatient mental health care facilities. The following exclusion criteria were used: 1) insufficient command of the Dutch language or insufficient capability to participate; 2) a primary clinical diagnosis of a psychiatric disorder other than depressive and anxiety disorders. Presence of depressive and/or anxiety disorders was established using the DSM-IV based Composite International Diagnostic Interview (CIDI, lifetime version)[49] and was conducted by trained research assistants. Baseline face-to-face assessments were completed by trained research assistants at participating centers between 2004 and 2007. Assessments were repeated after 2, 4, 6 and 9 years. Throughout this thesis, baseline and/or two-year data were used. At two-year follow up, 87.1% (N = 2,596) participated.

5.2 NETHERLANDS STUDY OF DEPRESSION IN OLDER PERSONS (NESDO)

NESDO's set-up, measurements and infrastructure were similar to NESDA, the largest difference being that NESDO was conducted among older persons. The NESDO sample at baseline consisted of 510 adults aged 60-93 years with a diagnosis of a current (6-month) depressive disorder (n = 378) or no history of depressive and anxiety disorders (n = 132). Recruitment took place in primary health care and both out- and inpatient mental health care facilities. Exclusion criteria were similar to those in NESDA, with one addition: (clinician-suspected) dementia, or having a Mini-Mental State Examination (MMSE)[50] score below 18 (out of 30). Baseline face-to-face assessments were completed

at participating centers between 2007 and 2010. Assessments were repeated after 2 and 6 years. Throughout this thesis, baseline and/or two-year data were used. At two-year follow-up, 78.6% (n = 401) still participated in NESDO.

5.3 MEASUREMENT OF KEY CONCEPTS IN THIS THESIS

5.3.1 MAJOR DEPRESSIVE DISORDER

Presence of current (6-month recency) and lifetime *MDD diagnoses* were determined using the Composite International Diagnostic Interview (CIDI, World Health Organization version 2.1, lifetime).[49] The CIDI was also used to determine duration of the longest depressive episode, age at onset of the first depressive episode, the number of depressive episodes so far, and presence of co-morbid dysthymia or any anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, and agoraphobia).

In order to measure *depression severity* and the *presentation of depressive symptoms*, the self-report Inventory of Depressive Symptoms (IDS-SR)[4] was used, a 30-item self-report questionnaire rated on a 0 to 3 scale, with a total score range from 0 to 84. This total score was used to measure depression severity. The 30 individual items, dichotomized into presence or absence of the symptom, were used to describe the presentation of depressive symptoms. In addition, three symptom clusters were created: a mood symptom cluster, a cognitive symptom cluster, and a somatic/vegetative symptom cluster.

To measure the *course of MDD,* in addition to the CIDI and the IDS-SR the Life Chart Interview[51,52] was used. Briefly, in the LCI, participants reported presence (yes/no) and severity (no or minimal severity, mild, moderate to severe, very severe) of depressive symptoms for each month of the two-year follow-up period. Symptoms were considered to be present when at least mild severity was reported. In this way, time to remission and the presence of a chronic symptom course could be established.

5.3.2 AGE

Chronological age was measured using standard questions. Throughout this thesis age was used as a continuous measure, but in order to provide insight of the course of depression at multiple time points throughout the adult life span, we sometimes provided information for several age categories. In this case, we either used three age categories (18-39 years, 40-59 years, 60+ years) or six age categories (18-39 years, 40-49 years, 50-59 years, 60-69 years, and 70+ years).

Biological age was indexed by leukocyte TL. Leukocyte TL was determined by Telomere Diagnostics, Inc. (TDx, Menlo Park, CA, USA) using fasting blood samples collected between 8:30 and 9:30 AM, which were subsequently stored at -80°C. Quantitative polymerase chain reaction (qPCR) was used to compare the telomere sequence copy number (T) in each patient's sample to a single-copy gene copy number (S), relative to a reference sample. The resulting T/S ratio was proportional to mean TL. A detailed description of the method is provided elsewhere.[43] To be able to compare the

T/S ratio to outcomes of TL from studies using Southern blot analysis (telomere restriction fragments, TRF), the T/S ratio was converted into base pairs (bp).

5.3.3 RISK FACTORS

Risk factors under study were socio-economic status (education, income), life stressors (childhood abuse, recent negative life events), personality (neuroticism, agreeableness, openness, conscientiousness and extraversion), reduced social functioning (social network size, loneliness, social support), unhealthy lifestyle (smoking, alcohol use, physical inactivity), and poor health (pain, BMI, and the number of chronic diseases). Risk factors were established using standard questions or using self-report questionnaires.

6 OUTLINE OF THIS THESIS

This thesis consists of two parts. **Part 1** consists of chapters 2-4 and is centered around the first general aim. In this part, the association between MDD and chronological age will be discussed. In **Chapter 2**, we examine whether the presentation of depressive symptoms differs across the age span. In **Chapter 3**, it is assessed whether a wide range of well-established risk factors for MDD is differentially associated with MDD during the life course. **Chapter 4** describes age differences in the two-year course of MDD. **Part 2** comprises chapters 5-7 and is focused on the association between MDD and biological age. In **Chapter 5**, we assess whether MDD and characteristics of MDD are associated with shorter TL. **Chapter 6** is focused on the association between early and recent negative life events and TL-shortening. In **Chapter 7** the association between TL and the two-year course of MDD is examined. Finally, in **Chapter 8**, a general concluding overview of this thesis is provided and findings are discussed. In addition, directions for future studies and clinical practice are provided.

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